CASE REPORT

Severe mycoplasma pneumoniae pneumonia combined with cold agglutinin disease and pulmonary embolism in childhood: A case report and review of the literature

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Abstract

This was a case report and literature review, aimed to strengthen the understanding and therapy of mycoplasma pneumoniae (MP) pneumonia combined with cold agglutinin disease and pulmonary embolism in children. A 7-year-old boy was taken to the hospital with fever for 7 days, cough for 5 days, and recurrent cyanosis at the extremities of one day duration. Pulmonary artery computed tomography angiography (CTA) showed pulmonary embolism, double pneumonia, and pleural effusion. Mycoplasma (MP) antibody IgM, Coombs test, and anti C3d were positive while anti-IgG was negative. After treatment, the patient improved. One month after discharge, the Coombs test was negative, and pulmonary CTA showed no pulmonary embolism. The diagnosis was severe MP with cold agglutinin disease and pulmonary embolism. The cases were reviewed, involving a total of 18 cases. Two patients had pulmonary embolism, and one had Raynaud's phenomenon with superior mesenteric artery and popliteal artery embolism. After treatment, 16 cases recovered while two cases were lost to follow up. We conclude that although the disease may be associated with severe complications such as embolism, acrocyanosis, and gangrene, the prognosis is relatively good for most patients. *(Afr J Reprod Health 2024; 28 [11]: 205-215).*

Keywords: Mycoplasma pneumonia, cold agglutinin disease, pulmonary embolism

Résumé

Il s'agissait d'un rapport de cas et d'une revue de la littérature visant à renforcer la compréhension et le traitement de la pneumonie à Mycoplasma pneumoniae (MP) associée à la maladie des agglutinines froides et à l'embolie pulmonaire chez les enfants. Un garçon de 7 ans a été transporté à l'hôpital avec de la fièvre depuis 7 jours, de la toux depuis 5 jours et une cyanose récurrente aux extrémités depuis une journée. L'angiographie par tomodensitométrie de l'artère pulmonaire (CTA) a montré une embolie pulmonaire, une double pneumonie et un épanchement pleural. Les anticorps IgM contre les mycoplasmes (MP), le test de Coombs et les anti C3d étaient positifs tandis que les anti-IgG étaient négatifs. Après traitement, l'état du patient s'est amélioré. Un mois après la sortie, le test de Coombs était négatif et le CTA pulmonaire ne montrait aucune embolie pulmonaire. Le diagnostic était une MP sévère avec maladie des agglutinines froides et embolie pulmonaire. Les cas ont été examinés, portant sur un total de 18 cas. Deux patients avaient une embolie pulmonaire et un avait un phénomène de Raynaud avec une embolie de l'artère mésentérique supérieure et de l'artère poplitée. Après traitement, 16 cas se sont rétablis tandis que deux cas ont été perdus de vue. Nous concluons que même si la maladie peut être associée à des complications graves telles qu'une embolie, une acrocyanose et une gangrène, le pronostic est relativement bon pour la plupart des patients. *(Afr J Reprod Health 2024; 28 [11]: 205-215).*

Mots-clés: Pneumonie à mycoplasmes, maladie des agglutinines froides, embolie pulmonaire

Introduction

Mycoplasma pneumoniae (MP) is an important pathogen of respiratory tract infections that can cause up community-acquired pneumonia in children[1]. In recent years, the number of refractory or severe cases with drug resistance has been gradually increasing[2]. In addition to pulmonary inflammation as the most common manifestation, MP may also cause damage to multiple systems and organs[3]. Importantly, there have been recent caseswhere MP pneumonia has led to both

pulmonary and extrapulmonary complications, such as pulmonary embolism and cold agglutinin disease[4,5]. Pulmonary embolism is an obstructive pulmonary artery caused by emboli in other parts of the body[6]. Risk factors for this condition include having a disease that may cause obstruction of venous return, or a disease that causes damage or dysfunction of the lining of the blood vessels, especially if the patient already has a tendency to have hypercoagulable blood[7].

The clinical manifestations of pulmonary embolism are varied, and common symptoms include shortness of breath, chest pain, and in some severe patients, mild headache, presyncope, syncope, and even cardiac or respiratory arrest may occur[8]. The most commonly used imaging test to diagnose pulmonary embolism is computed tomography angiography (CTA), which is sometimes combined with a pulmonary ventilation/perfusion scan to confirm pulmonary embolism[9]. Pulmonary embolism is mainly treated with anticoagulants, and depending on the patient, systemic thrombolysis or catheter-guided thrombolysis, catheter aspiration thrombectomy, or surgical resection may be used to directly remove the clot[10]. Cold agglutinin disease also known as cold agglutinin syndrome, is a group of diseases characterized by the presence of autoreactive erythrocyte lectins that significantly increase their activity at below normal body temperature, leading to hemolytic anemia and/or microcirculation infarction[11]. Cold agglutinin disease can be divided into primary and secondary[12]. Secondary lectins are associated with infections, autoimmune diseases, and lymphomas, while primary lectins are often idiopathic[13]. Treatment of secondary cold agglutinin disease involves treating the underlying cause and supportive care[14]. The most common associated infectious agents that cause cold agglutinin disease include MP and Ebstein-Barr virus[15].

The presented study reported a case of a child with severe MP pneumonia combined with cold agglutinin disease and pulmonary embolism. Our clinical experience may improve clinicians' understanding of the disease.

Case data

General data

A 7-year-old boy was taken to The Affiliated Yantai Yuhuangding Hospital of Qingdao University on January 9, 2019 due to "fever for 7 days, cough for 5 days, and recurrent cyanosis at the extremities for one day." The boy presented with recurrent high fever and paroxysmal non-spastic cough outside the hospital. He was treated with "intravenous drip of cephalosporin antibiotics and azithromycin" for three days, without improvement. One day before admission, he had cyanosis in both extremities, which was relieved after warming, but it re=occurred. Thereafter, he was referred to our hospital. Routine blood examination showed white blood cells of 25.2×10^9/L, neutrophils were 82.6%, red blood cells were 4.3×10^{12}/L, hemoglobin was 127 g/L, and C=reactive protein (CRP) was 94 mg/L. Chest X-ray showed bilateral lower pneumonia with bilateral pleural effusion (a small amount).

There was no family history of anaemia or embolic disease. Physical examination showed the following: temperature was 38.1℃; pulse was 140 beats/min, respiration was 40 beats/min, oxygen saturation was 94%, and his weight was 24.5 kg. He had slight shortness of breath, negative inspiratory three concave sign, thick breath sound in left lung, as well as lower breathing sound of the right lung than those of the left lung. No dry or wet rales were heard in both lungs, while heart and abdomen examinations were normal. The extremities were cool and cyanosed, but the dorsalis pedis artery beat was normal.

Venous blood (EDTA tube) was drawn on the day of admission, and "blood clot" was observed on the wall of the tube. The results of the routine blood examination were as follows: white blood cells was 17.2×10^9/L, neutrophils 79.6%, red blood cells 1.2×10^{12}/L, hemoglobin 103 g/L, platelets 446×10^9/L and C-reactive protein (CRP) was 165.8 mg/L. Mycoplasma pneumoniae (MP) antibody IgM was positive, titer was 1:320. Coagulation function showed that D-dimer was 3.6 mg/L, but normal.

Biochemical series showed that albumin was 31.1 g/L, lactate dehydrogenase (LDH) was 469 U/L, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin and indirect bilirubin were normal.

On the second day of hospitalization, the boy had blood in the sputum, accompanied by right chest pain, shortness of breath, 56 beats/min of respiratory rate, and positive inspiratory triple concave sign. Pulmonary artery computed tomography angiography (CTPA) was consistent with the CTA manifestations of pulmonary embolism, double pneumonia, and right-sided pleural effusion. Blood routine examination showed that white blood cells were 11.3×10^9/L, neutrophils 77.0%, red blood cells 1.1×10^{12}/L, haemoglobin 88 g/L, haematocrit 21.8%↑, mean red blood cell volume 92.8 fL↑, mean hemoglobin volume 42.6 pg↑, mean hemoglobin concentration was 459 g/L↑, platelet was 652×10^9/L and CRP was 36.9 mg/L.

Venous blood (EDTA tube) was taken, and "blood clot" was visible on the wall of the tube. The sample was heated to 37℃, and the blood clot was found to have disappeared. The blood routine examination of the sample showed that the red blood cells were 2.7×10^{12}/L, the hemoglobin was 89 g/L, and the white blood cells, neutrophils, and platelets had no significant changes. Cold agglutinin test was 1:256. Reticulocyte was 5.1%, direct anti-human globulin test and Coombs test were positive, anti-C3d was positive, anti-igG was negative. Ferritin was 573.2 g/ml, vitamin B12, folic acid and iron test were normal. Antithrombin III, protein S and protein C were normal. The autoantibody test was negative. Three antiphospholipid antibody tests showed negative anticardiolipin antibody IgG. Anticardiolipin antibody IgM and anti-β2-glycoprotein 1 were positive. EB-IgM and EB-DNA were negative. T cell tests for TB infection were negative.

After admission, the cyanosis of extremities was relieved after keeping warm. Cefotiam combined with azithromycin was used to control infection. Methylprednisolone sodium succinate (4 mg/kg.d) was used to inhibit inflammatory response. Intravenous immunoglobulin (IVIG, 1 g/kg per times ×2 days) was used to alleviate hemolysis. Low molecular weight heparin subcutaneous injection and oral warfarin were administered for anticoagulation. On the fourth day of hospitalization, the body temperature dropped to normal, and the symptoms such as cough, chest pain, and dyspnea gradually relieved. On the 7th day of hospitalization, the blood routine examination displayed that white blood cell was 12.4×10^9/L, neutrophil was 58.8%, red blood cell was 3.6×10^{12}/L, hemoglobin 121 g/L and CRP 5.4 mg/L. Reticulocyte was 2.1%. D-dimer was 1.0 mg/L. The boy was hospitalized for 13 days with normal body temperature, stable breathing but with occasional cough. Blood routine examination showed that white blood cell was 8.9×10^9/L, neutrophil was 50%, red blood cell was 3.5×10^{12}/L, haemoglobin was 119 g/L, platelet 472×10^9/L and CRP 1.1 mg/L. The condition of the boy was improved and he was discharged. After discharge, oral prednisone and warfarin were continued to take orally. The reexamination of Coombs test was negative one month after discharge. Antiphospholipid antibodies were negative for all three. Chest CTPA was reexamined 3 months after discharge, and no pulmonary embolism was found. According to the child patient's medical history, clinical manifestations, and auxiliary examinations, the child was diagnosed as severe MP pneumonia with cold agglutinopathy and acute pulmonary embolism.

Literature review

From the establishment of the database to May 2022, CNKI, Wanfang database and PubMed database were used to search literatures, and the key words included "Mycoplasma pneumonia, cold agglutinin disease" and "Mycoplasma pneumonia, cold agglutinin disease". Seventeen case reports with complete clinical data were excluded, including 5 Chinese literatures and 12 English literatures. According to the above literature statistics, there were a total of 18 cases, including 2 children and 16 adults. The age of patients ranged from 8 to 66 years, with a median age of 33.4 years.

All cases were positive for MP antibody. Based on the lung signs and lung related imaging examinations, all cases were in accordance with the

diagnosis of MP pneumonia. The time of diagnosis of cold agglutinin disease was 7-21 days. The main manifestations were anemia, yellow staining of the skin and sclera. One case showed Raynaud's phenomenon, accompanied by superior mesenteric artery and popliteal artery embolism, three cases had pulmonary embolism, two cases had lymph node enlargement, and one patient had myocardial infarction together with cardiac insufficiency.

The details of each literature are shown in Table 1. Laboratory tests showed that all cases had anemia, including 13 cases with mild to moderate anemia and 5 cases with severe and extremely severe anemia. The bilirubin level was slightly raised in 13 cases, normal in two cases, and unknown in the remaining 3 cases. Lactate dehydrogenase level was not known in 4 patients, but was significantly elevated in the other 14 patients. The cold agglutinin titer was not recorded in 5 cases, one case was in the normal range of 1:8, and the remaining 12 cases showed varying degrees of increase in cold agglutinin titer, ranging 1: (64-20480). Erythrocyte agglutination appeared on blood smears or blood vessel walls in 13 patients, and some patients showed heterocytic cells and megakaryocytes. The direct anti-human globulin test was positive in all cases except 2 cases, among which 9 cases were only positive for anti-C3d antibody and negative for anti-IgG antibody, and 2 cases were positive for anti-C3d antibody and anti-IgG antibody. The details of each literature were displayed in Table 2. Among the 18 patients, 15 received macrolide antibiotics. Ten patients accepted glucocorticoid. Five patients with severe and extremely severe anemia were transfused with heated red blood cells. Two patients accepted plasma exchange, and two patients accepted intravenous immunoglobulin (IVIG). After active treatment, except two cases without follow-up, the other 16 patients were cured. The patient was cured followed by treatments with azithromycin, methylprednisolone sodium succinate, and gamma globulin.

Discussion

MP infection belongs to one of the common pathogens in children's respiratory system infection, and MP pneumonia accounts for about 10%-40% of children's community-acquired pneumonia[33].

It is often complicated with various intrapulmonary and extrapulmonary complications, of which about 25% can be complicated with extrapulmonary complications, which generally occurs 2 days to several weeks after infection, and can involve various systems of the whole body, such as the skin and mucous system, nervous system, cardiovascular system, digestive system, and blood system.

However, there are few reports on cold agglutinin disease after MP infection, especially in children. This paper reported a case of severe MP infection complicated with cold agglutinin disease and pulmonary embolism in children, and analyzed the literature retrospectively to improve the understanding and treatment of this disease.

Cold agglutinin disease (CAD) is a group of diseases caused by autoantibodies (mainly immunoglobulin M), which belongs to a type of cold anti-type autoimmune hemolytic anemia. It is rare in clinical practice, accounting for 15%-25% of autoimmune hemolytic anemia. Among them, immune hemolytic anemia in children accounts for about 10%[34]. According to the etiology, it can be divided into primary and secondary.

Secondary cases are more common in autoimmune diseases, hematological malignancies (such as lymphoma), after hematopoietic stem cell transplantation and after infection (such as mycoplasma, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus (HIV), legionella, varicella, citrobacter, mumps, varicella, rubelladenovirus, influenza and hepatitis C)[35]. A child with cold agglutinin disease after MP infection was described in this paper.

Table 1: Clinical data, treatment and prognosis of the cases were reported in the literature

Serial number	Age	CAD time	Physical signs of lung	Pulmonary imaging examination	Extra pulmonary manifestations and complications	Macrolide	Treatment with glucocorticoids	Other treatments	Outcome
1[16]	29	21	Wet rale in left lung	Left lower pneumonia, a small amount of pleural effusion on the right	Nothing	Azithromycin	Use (unknown)	Nothing	Cure
2[17]	54	15	Wet rale in both lungs	Changes of bronchopneumonia	Lymphadenectasis	Azithromycin	Unuse	Nothing	Cure
3[18]	28	16	Wet rale in both lungs	Unclear	Anemic appearance, yellow skin	Azithromycin	Prednisone tablets	Nothing	Unclear
4[18]	18	14	Decreased breath sounds	There was a large consolidation of the right lung and pleural effusion	Anemic appearance	Azithromycin	Methylpredniso lone	Nothing	Unclear
5[19]	27	14	Wheezing in both lungs	Consolidation of lower lobes of both lungs. Right lower pulmonary artery embolism	Anemic appearance, sclera yellow staining	Moxifloxacin	Methylpredniso lone	Nothing	Cure
6[20]	25	10	Twirling of the lungs	Patchy shadow in the left lung	Nothing	Unclear	Unuse	Nothing	Cure
7[21]	29	8	Twirling of the lungs	The base of both lungs was exudate	Anemia, yellow skin, dark urine	Azithromycin	Unuse	Nothing	Cure
8[22]	9	10	Decreased breath sounds	Lobar pneumonia	Anemic appearance, tachycardia	Clarithromycin	Unuse	Heated red blood cells + IVIG	Cure
9[23]	40	14	Decreased breath sounds	Infiltrating shadow in the right lower lobe	Raynaud phenomenon, Superior mesenteric artery and popliteal artery embolism	Azithromycin	Methylpredniso lone	Heated red blood cells, plasma exchange	Cure

10[24]	8	7	Unclear	Consolidation in the middle and lower lobe of the left lung	The fluctuation of dorsalis pedis, posterior tibial artery and popliteal artery of both lower limbs disappeared and gangrenous	Azithromycin	Methylprednisolone	Amputation	Cure
11[25]	66	21	Wet rale in right lung	Bilateral pleural effusion. Enlarged mediastinal lymph nodes	Lymphadenectasis	Clarithromycin	Unuse	Heated red blood cells	Cure
12[26]	44	10	Low breath sounds in the right lung	Focal patchy consolidation in the upper lobe of the right lung	Nothing	Clarithromycin	Unuse	Nothing	Cure
13[27]	39	7	Wet rale in both lungs	No abnormalities	Yellow skin, dark urine	Unclear	Prednisolone	Nothing	Cure
14[28]	27	10	Twirling of the lungs	Double pneumonia. Right middle lobe artery embolism.	Anemic appearance, yellow skin	Ciprofloxacin	Prednisone tablets	Heated red blood cells	Cure
15[29]	49	14	Rales in both lungs	There were interstitial changes at the base of both lungs	Myocardial infarction, cardiac insufficiency	Unclear	Methylprednisolone	Heated red blood cells	Cure
16[30]	29	15	Wet rale in left lung	Patchy exudative lesion in the left lower lung	Nothing	Moxifloxacin	Unuse	Nothing	Cure
17[31]	31	10	Wet and dry rale	There was a large consolidation in the left lung and patchy shadow in the upper lobe of the right lung	Anemia, yellow skin, dark urine	Moxifloxacin	Methylprednisolone	IVIG+plasma exchange	Cure
18[32]	50	10	Unclear	Patchy infiltrates of the left lung with effusion	Anemic appearance, yellow skin	Roxithromycin	Unuse	Concentrated erythrocyte	Cure

Table 2: Laboratory data of cases reported in the literature

Serial number	Minimum hemoglobin (g/L)	Total/direct bilirubin	LDH (U/L)	Cold agglutinin (titer)	Blood smear	Mycoplasma pneumoniae antibody and titer	Direct anti-human globulin test Anti-c3d/anti-igg
1[16]	104	Normal range	381.4	1:1024	Unclear	Positive	Positive (unclassified)
2[17]	96	46.9/38	Unclear	1:256	There was red blood cell agglutination in the tube wall	Positive	Positive/Negative
3[18]	68.5	37.3/11.1	635	1:20480	Autocoagulation of red blood cells in vessel walls	Positive (1:640)	Positive/Negative
4[18]	76.3	28.3/12.1	1409	Unclear	Unclear	Positive (1:1280)	Positive/Negative
5[19]	86	47/2	Unclear	1:8	There was autocoagulation of red blood cells in the wall	Positive (1:320)	Positive (unclassified)
6[20]	94	2.8/0.3	Unclear	1:256	Erythrocytes agglutinate, moderately heterocytoid and few spheroid erythrocytes	Positive	Strong positive (unclassified)
7[21]	63	64/43.8	2758	Unclear	Leukocytosis and erythrocyte agglutination	Positive (1:1:240)	Strong positive (unclassified)
8[22]	56	30.8/23.9	1277	1:1024	Red blood cell agglutination, heterogeneous red blood cell size, heteromorphic/normal red blood cell, megakaryocyte platelet	Positive	Positive/Negative
9[23]	76	47.9/Unclear	760	1:128	Unclear	Positive (1:256)	Unclear
10[24]	95	Unclear	1218	1:1024	Red blood cell agglutination	Positive	Positive/Negative
11[25]	70	29/Unclear	643	Unclear	Lots of lectins, giant plates, target cells	Positive	Positive/Negative
12[26]	84	Unclear	639	Unclear	Erythrocyte agglutination, polymorphous megakaryocytes,	Positive	Positive/Negative

					nucleated red cells, heterotypic lymphocytes		
13[27]	80	35/8	57.3	1:64	Unclear	Positive (1:640)	Weak positive (unclassified)
14[28]	40	105/Unclear	Unclear	Unclear	Erythrocyte agglutination, thrombocytosis and uneven size	Positive	Positive/Negative
15[29]	Severe	Unclear	638	1:4096	Spherical erythrocytes and basophils	Positive	Positive/Negative
16[30]	83	16.3/3.7	653	1:256	Red blood cell agglutination	Positive	Positive/Negative
17[31]	32	73.9/47.4	1388	1:512	Red blood cell agglutination	Positive	Positive/Negative
18[32]	41	33.7	884	1:1024	Unclear	Positive	Unclear

At present, the pathogenesis of cold agglutinin disease after MP infection is considered to be related to immune dysfunction and hypercold agglutinemia after infection. Cold agglutinin antibody, mainly immunoglobulin M, is produced 1-3 weeks after MP infection, which bind to red blood cell surface antigen I/i and cause red blood cells to aggregate under low temperature conditions (0-4℃).

When the temperature is 20-25℃, it binds to complement, starts the classical complement pathway, and damage red blood cells, resulting in microvascular blood stasis, intravascular and/or extravascular hemolysis, resulting in different degrees of anemia (mainly mild to moderate), jaundice, and post-infection erythrocyte agglutination related symptoms containing acrocyanosis, deep purple and gray skin at the distal end of the limb, ear and nose, and symptoms can disappear after warming. In severe cases, skin necrosis and gangrene may even occur[24,36]. Direct anti-human globulin test showed type C3d antibody was positive. Peripheral blood smear showed red blood cell aggregation. At the same time, incorrectly increased MCH and MCHC and incorrectly decreased total number of red blood cells can also occur[37,38]. CAD after MP infection is self-limited. Most patients can be cured by treatment of primary infection and symptomatic and supportive treatment (warming, transfusion of heated red blood cells, IVIG), and it is not easy to relapse. However, the effects of glucocorticoid and plasma exchange are not clear. In this paper, the child patient was diagnosed with severe mycoplasma pneumonia, and was treated with azithromycin anti-mycoplasma therapy, keeping warm and IVIG, and glucocorticoid to suppress the inflammatory reaction, and the condition gradually stabilized. In the case reports with complete clinical data, the main manifestations were mild to moderate anemia and mild elevation of bilirubin. Most of the treatment of the original disease and symptomatic treatment, improved and recovered.

The occurrence of thromboembolic diseases is mainly related to vascular endothelial injury, hemodynamic changes and hypercoagulable state of blood. A recent study[39] showed that patients with cold agglutinin disease have an increased risk of thrombosis compared with the general population (relative risk 1.7-2.4), but the pathological mechanism is not clear. A literature review published in 2016 elucidated the relationship between cold agglutinin and mycoplasma and pulmonary embolism. Although the mechanism behind this association is not clear, the increase in blood viscosity caused by cold agglutinin may be the reason[40]. In addition, Michelle L. Wilson[23] has proposed that the occurrence of recurrent superior mesenteric artery embolism and popliteal artery embolism may be related to vascular endothelial injury caused by vasculitis, and the occurrence of vasculitis is considered to be a complication of MP infection. In this case, the D-dimer of the patient presented higher than normal, and obvious blood agglutination was found after blood drawing, indicating the existence of hypercoagulable state. Therefore, it was considered that the occurrence of pulmonary embolism was related to the hypercoagulable state of blood, and the patient recovered after treatment of the primary disease and anticoagulant treatment. In the retrospective analysis, 3 cases of MP infection, cold agglutinin disease and thromboembolic disease were also found[19,23,28]. Two of the three patients had pulmonary embolism, and were treated with quinolones for the primary disease, glucocorticoids to suppress the inflammatory response and low molecular weight heparin anticoagulation therapy. The other case was accompanied by superior mesenteric artery embolism and popliteal artery embolism. Although treated with macrolide antibiotics and glucocorticoids, the effect was poor, and the clinical symptoms were relieved and cured after plasmapheresis and surgical treatment.

Conclusion

When patients with MP pneumonia have acrocyanosis, red blood cell agglutination, and disproportionate changes in the relationship between hemoglobin decline and red blood cells, MCV, and MCHC, secondary cold agglutinin disease should be vigilant, and the primary disease should be actively treated to avoid further progression of the disease, severe hemolytic anemia, gangrenia, and other

serious complications. It should pay attention to the symptoms of children, dynamic monitoring of coagulation function, if necessary, preventive use of anticoagulant drugs, to prevent the occurrence of thromboembolic diseases.

Contribution of authors

Liang S and Liu HB: conceived and designed the study, collected and analysed the data, and prepared the manuscript. All authors mentioned in the article approved the manuscript..

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